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Review Article

A REVIEW ON TINIDAZOLE

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ABSTRACT

Tinidazole, a synthetic nitroimidazole, a structural analogue of metronidazole, is an antiprotozoal agent that has been widely used for more than two decades with established efficacy and acceptable tolerability for the treatment of trichomoniasis, giardiasis, amebiasis, and amebic liver abscess. Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon but also for its potential for the delivery of proteins and therapeutic peptides.

Keywords: Tinidazole, Trichomoniasis, Colon targeted, Osmotic drug delivery system.

INTRODUCTION

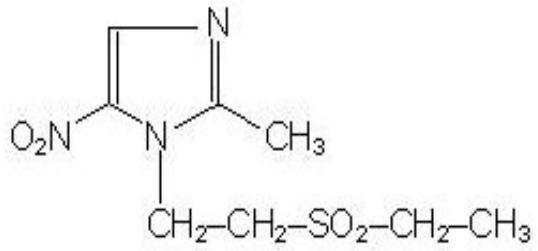
Tinidazole, a synthetic imidazole derivative, is widely used in the oral treatment of several protozoal infections - trichomoniasis, giardiasis and amoebiasis. Among the protozoal organisms inhibited by tinidazole are *Trichomonas vaginalis, Trichomonas foetus*, and *Entamoeba histolytica*.[1] Tinidazole is the most preferred choice of drug for intestinal amoebiasis. This drug is to be delivered to the colon for its effective action against *Entamoebe histolytica* where in the trophozoites reside in the lumen of the caecum and large intestine and also adhere to the colonic mucus and epithelial layers. But the pharmacokinetic profile of tinidazole indicates that the drug is completely and promptly absorbed after oral administration[2]. The administration of this drug in conventional tablet dosage form provides minimal amount of tinidazole for local action in the colon, still resulting in the relief of amoebiasis, but with unwanted systemic effects. Thus there is strong clinical need and market potential for a delivery system that will deliver maximum amount of tinidazole to the colon in controlled manner[3].

DRUG PROFILE

Generic Name: Tinidazole

- IUPAC Name: 1-[2-(ethylsulfonyl)ethyl]-2-methyl-5-nitroimidazole.
- Molecular formula: $C_8H_{13}N_3O_4S$

- Structural Formula:



Tinidazole pronounced as: tie-NIH-dah-zole[4]

Physicochemical properties of Tinidazole

- Description: White or pale yellow crystalline powder
- Molecular weight: 247.27g/mol
- Solubility: Practically insoluble in water, soluble in acetone and in methylene chloride, sparingly soluble in methanol.
- Log P: 0.7
- Functional category: Antiprotozoal, Antibacterial.

Storage conditions: Store at controlled room temperature 20-25° C (68-77° F); excursions permitted to 15-30° C (59-86° F). Protect from sunlight and moisture.[5-6]

PHARMACOKINETICS

- Bioavailability: 88 and 129% with a mean of 99% (single oral dose)
- Biological half life: 12-14 hrs
- Route of administration: Oral
- Protein binding: 12%
- Metabolism: Oxidation, hydroxylation, conjugation
- Route of elimination: Liver and kidneys[5-6]

Absorption

Absorbs rapidly and completely under fasting conditions. Oral absorption of tinidazole is found to be 100%.[7]

Distribution

Distributes to virtually all tissues and body fluid and crosses the blood-brain barrier. The apparent volume of distribution is about 50 L. Protein binding is 12%.

Metabolism

Tinidazole is significantly metabolized in humans prior to excretion. Tinidazole is partly metabolized by oxidation, hydroxylation and conjugation. Tinidazole is the major drug-related constituent in plasma after human treatment, along with a small amount of the 2-hydroxymethyl metabolite. Tinidazole is biotransformed mainly by CYP3A4. In an in vitro metabolic drug interaction study, tinidazole concentrations of up to 75 µg/mL did not inhibit the enzyme activities of CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2E1, and CYP3A4.[8]

Excretion

The plasma half-life of tinidazole is approximately 12-14 hours. Tinidazole is excreted by the liver and the kidneys. Tinidazole is excreted in the urine mainly as unchanged drug (approximately 20-25% of the administered dose). Approximately 12% of the drug is excreted in the feces.

Mechanism of Action

Tinidazole is an antiprotozoal, antibacterial agent. The nitro-group of tinidazole is reduced by cell extracts of trichomonas. The free nitro-radical generated as a result of this reduction may be responsible for the antiprotozoal activity. Chemically reduced tinidazole was shown to release nitrites and cause damage to purified bacterial DNA in vitro. Additionally, the drug caused DNA base changes in bacterial cells and DNA strand breakage in mammalian cells. The mechanism by which tinidazole exhibits activity against Giardia and Entamoeba species is not known.[9]

ANTIBACTERIAL ACTIVITY

Culture and sensitivity testing of bacteria are not routinely performed to establish the diagnosis of bacterial vaginosis; standard methodology for the susceptibility testing of potential bacterial pathogens, *Gardnerella vaginalis*, Mobiluncus spp. or *Mycoplasma*

hominis, has not been defined. The following in vitro data are available, but their clinical significance is unknown. Tinidazole is active in vitro against most strains of the following organisms that have been reported to be associated with bacterial vaginosis:

- Bacteroides spp.
- *Gardnerella vaginalis*
- Prevotella spp.

Tinidazole does not appear to have activity against most strains of vaginal lactobacilli.

ANTIPROTOZOAL ACTIVITY

Tinidazole demonstrates activity both in vitro and in clinical infections against the following protozoa: *Trichomonas vaginalis*, *Giardia duodenalis* (also termed *Giardia lamblia*), and *Entamoeba histolytica*.

DOSAGE AND ADMINISTRATION

Dosing Instructions

It is advisable to take tinidazole with food to minimize the incidence of epigastric discomfort and other gastrointestinal side-effects. Food does not affect the oral bioavailability of tinidazole.[10] Alcoholic beverages should be avoided when taking tinidazole and for 3 days afterwards.

Dose in Trichomoniasis

The recommended dose in both females and males is a single 2 gm oral dose taken with food. Since trichomoniasis is a sexually transmitted disease, sexual partners should be treated with the same dose and at the same time.

Dose in Giardiasis

The recommended dose in adults is a single 2 gm dose taken with food. In pediatric patients older than three years of age, the recommended dose is a single dose of 50 mg/kg (up to 2 gm) with food.

Dose in Amebiasis

In adults a dose of 2 gm daily for 3 days with food is recommended. Children older than 3 years of age, the recommended dose is 50 mg/kg daily (max, 2 gm/day) for 3 days with food. In amebic liver abscess adults, the recommended dose is 2 gm dose daily for 3 to 5 days with food.

Dose in Bacterial Vaginosis

The recommended dose in non-pregnant females is a 2 gm oral dose once daily for 2 days taken with food or a 1 gm oral dose once daily for 5 days taken with food. The use of tinidazole in pregnant patients has not been studied for bacterial vaginosis.

Treatment of Overdosage

There is no specific antidote for the treatment of overdosage with tinidazole; therefore, treatment should be symptomatic and supportive. Gastric lavage may be helpful. Hemodialysis can be considered because approximately 43% of the amount present in the body is eliminated during a 6 hour hemodialysis session.

Drug interactions

- Azole antifungals (eg, ketoconazole) or cimetidine because they may increase the risk of tinidazole's side effects
- Barbiturates (eg, phenobarbital), phenytoin, or rifampin because they may decrease tinidazole's effectiveness
- Anticoagulants (eg, warfarin), astemizole, busulfan, cisapride, cyclosporine, fluorouracil, lithium, macrolide immunosuppressants (eg, tacrolimus), sulfonylureas (eg, glipizide), or terfenadine because their actions and the risk of their side effects may be increased
- Disulfiram because side effects, such as mental or mood changes, may occur
- Oral contraceptives (birth control pills) because their effectiveness may be decreased by tinidazole.

POTENTIAL EFFECTS OF OTHER DRUGS ON TINIDAZOLE

CYP3A4 Inducers and Inhibitors

Simultaneous administration of tinidazole with drugs that induce liver microsomal enzymes, i.e., CYP3A4 inducers such as phenobarbital, rifampin,

phenytoin, and fosphenytoin (a pro-drug of phenytoin), may accelerate the elimination of tinidazole, decreasing the plasma level of tinidazole.

Cholestyramine
Cholestyramine shows decrease in the oral bioavailability of metronidazole by 21%. Thus, it is advisable to separate dosing of cholestyramine and tinidazole to minimize any potential effect on the oral bioavailability of tinidazole.

Oxytetracycline
Oxytetracycline was reported to antagonize the therapeutic effect of tinidazole.

USE IN SPECIFIC POPULATIONS
Pregnancy
As tinidazole crosses the placental barrier and enters fetal circulation it should not be administered to pregnant patients in the first trimester.

Nursing Mothers
Tinidazole is excreted in breast milk in concentrations similar to those seen in serum. Tinidazole can be detected in breast milk for up to 72 hours following administration. Interruption of breast-feeding is recommended during tinidazole therapy and for 3 days following the last dose.

Pediatric Use
Other than for use in the treatment of giardiasis and amebiasis in pediatric patients older than three years of age, safety and effectiveness of tinidazole in pediatric patients have not been established. For those unable to swallow tablets, tinidazole tablets may be crushed in artificial cherry syrup, to be taken with food.

Renal Impairment
Because the pharmacokinetics of tinidazole in patients with severe renal impairment (CrCL< 22 mL/min) are not significantly different from those in healthy subjects, no dose adjustments are necessary in these patients.

Patients undergoing hemodialysis: If tinidazole is administered on the same day as and prior to hemodialysis, it is recommended that an additional dose of tinidazole equivalent to one-half of the recommended dose be administered after the end of the hemodialysis.[11-12]

Side effects
The most common side effects reported with tinidazole are upset stomach, bitter taste, diarrhoea and itchiness. Other side effects which occur are headache, physical fatigue, and dizziness. Drinking alcohol while taking tinidazole causes an unpleasant disulfiram-like reaction, which includes nausea, vomiting, headache, increased blood pressure, flushing and shortness of breath.

DRUG DELIVERY SYSTEMS
Colon targeted delivery systems are well recognized and documented to deliver most of the drugs to colon. In the past, various primary approaches for colon targeted delivery, such as, prodrugs approach, pH, time and pressure dependent systems, have achieved limited success. Osmotic drug delivery system (ODDS) utilizes the principle of osmotic pressure for controlled delivery of drugs[13-15]. Drug release from these systems is independent of pH and other physiological parameter to a large extent and exhibit significant *in-vitro–in vivo* correlation. Drug delivery from ODDS follow zero-order kinetic hence provides better control over *in-vivo* performance. Various types of osmotic pumps have been reported to target the drug to colon for local or systemic therapy. These systems were essentially time dependent systems. High variation of gastric retention time makes these systems complicated in predicting the accurate location of drug release.

USES
Tinidazole is used in the treatment of following conditions like Bacterial vaginosis, Endometritis, Dental infections, In combination with other antibiotic to treat H.pylori infection in peptic ulcer disease, Post

operatively for anaerobic infections, Protozoan infection like Giardiasis, Trichomoniasis, Hepatic & intestinal amoebiasis, Skin and soft tissue infections,Peritonitis, Pneumonia and Lung abscess.

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